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MINI-REVIEW

Key insights into secondary metabolites from various *Chaetomium* species

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Abstract

Endophytic fungi have proved to be a major source of secondary metabolites, wherein the genus *Chaetomium* has emerged as a source of multifarious bioactive natural compounds belonging to diverse classes such as chaetoglobosins, epipolythiodioxopiperazines, azaphilones, xanthones, anthraquinone, chromones, depsidones, terpenoids, and steroids. The objective of this review is to encapsulate recent findings on various *Chaetomium* strains, such as *C. globosum*, *C. cupreum*, *C. elatum*, *C. subspirale*, *C. olivaceum*, *C. indicum*, and *C. nigricolor* known for production of beneficial secondary metabolites, with an insight into their origin and function. A thorough literature survey was conducted for obtaining *Chaetomium*-derived secondary metabolites, with a scope of future application into drug development efforts. More than 100 secondary metabolites, with various beneficial properties such as antitumor, cytotoxic, antimalarial, and enzyme inhibitory activities, were enlisted. We believe this review will enhance the understanding of beneficial effects conferred by various *Chaetomium*-derived secondary metabolites and emphasize their potential in serving novel drug development efforts.

Key points

- *Identified Chaetomium-derived metabolites with potential for drug development.*
- *More than 100 beneficial metabolites are enlisted.*
- *Benefits include anti-cancerous, antimalarial, and anti-enzymatic properties.*

Keywords Chaetomium · Endophytes · Drug discovery · Natural products · Bioactivities

Introduction

Natural compounds offer a great alternative in the human quest for disease curing medicines. In drug development research, secondary metabolites and their derivatives obtained from plants, bacteria, marine, and animal sources serve as attractive components of new drugs in the fields of microbial chemistry, biology, and medicine. As compared to synthetic drugs, these naturally derived drugs have better structural diversity, complexity, persistent nature and exhibit a wide range of biological activities (Atanasov et al. 2021; Dwibedi et al. 2022).

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Endophytic fungi have a huge potential as a source of bioactive compounds (Dwibedi and Saxena 2018; Keller 2019). They have adapted to life inside the tissues of other eukaryotes, which might trigger biosynthesis of novel secondary metabolites with potent bioactivity (Dwibedi and Saxena 2020; Rokas et al. 2020). A myriad of endophyte-derived, secondary metabolites belonging to diverse chemical classes like phenolic acids, phenylpropanoids, cytochalasins, alkaloids, isocoumarins, steroids, furandiones, terpenoid derivatives, flavonoids, quinones, lignans, peptides, and aliphatic compounds have been reported (Ancheeva et al. 2020; Dwibedi and Saxena 2019; Torres-Mendoza et al. 2020). These metabolites are well known for their antioxidant, antibiotic, antiviral, anti-diabetic, immunosuppressive, anticancer, and insecticidal properties (Dwibedi and Saxena 2019; Torres-Mendoza et al. 2020). Recently, several novel bioactive compounds have been isolated from fungal endophytes, including xylarosides, penicidones, xylariol, and benzoquinone derivatives (Poveda et al. 2022).

Various reports enlist the secondary metabolites, isolated from different endophytic fungi and their biological applications. Rustamova et al. (2020) summarized nearly 220 biologically relevant metabolites, including meroterpenoids, sesquiterpenoids, polyketides, and steroids, isolated from various endophytic fungi genus, such as *Alternaria*, *Ascomycota*, *Cerrena*, *Cytospora*, *Fusarium*, *Mucor*, *Preussia*, *Trichoderma*, and *Xylaria* (Rustamova et al. 2020). In 2021, Cao et al. reviewed nine strains of various endophytic fungi (*Penicillium* sp. *LDL4.4*, *Colletotrichum gloeosporioides* ESO26 and Cg01, *Alternaria brassicae* AGF041, *Penicillium polonicum* hy4, *Shiraia* sp. Slf14, *Paecilomyces tenuis* YS-13, *Trichoderma harzianum* L44, *Colletotrichum cladosporioides* LF70, and *Ceriporia lacerate* HS-ZJUT-C13A), isolated from *Huperzia serrata*, that can produce Huperzine A, a known acetylcholinesterase inhibitor (Cao et al. 2021). In an interesting review from University of Panama and Institute for Scientific Research and Technology Services, Panama, the authors enlisted endophytic fungi-derived secondary metabolites with a novel, uncommon structure (Ortega et al. 2021). These compounds, including cytochalasans, indole alkaloids, pyridine derivatives, and peptides, were known for various biological activities, such as antitumor, antiviral, and anti-inflammatory activities (Ortega et al. 2021).

In 1817, Gustav Kunze discovered the genus *Chaetomium*, an endophytic fungal genus in the family *Chaetomiaceae* (Abdel-Azeem 2019). It is a dark-walled mold normally found in soil, air, plant, and cellulose debris. *Chaetomium* occurs in a wide variety of substrates that have gained attention for their ability to generate a spectrum of biologically active compounds (Salo et al. 2020). According to the *Fungi* dictionary, the widespread genus includes about 95 species. *Chaetomium* is characterized by ostiolate ascomata, covered with hair, or setae and clavate, fusiform or cylindrical, fascicular, evanescent asci, and brown to gray-colored, single-celled ascospores with one or two germ pores. *Chaetomium* has been related to many anamorphic genera such as *Acremonium*, *Botryotrichum*, *Chrysosporium*, *Histoplasma*, *Humicola*, *Phialophora*, *Scopulariopsis*, and *Scytalidium*. More than 400 species have been described since the creation of the genus, many of which have been synonymized/excluded, and only 273 *Chaetomium* species have been recognized under the Index Fungorum Partnership (Abdel-Azeem 2020; Calaça et al. 2020). *Chaetomium* sp., due to the variety of species and habitats, can activate different clusters of biosynthetic genes, thus expressing different bioactive compounds to adjust to various ecosystems. Over 200 compounds with a broad range of bioactive effects have been isolated from *Chaetomium* sp. so far (Table 1) (Elkhateeb et al. 2021), yet more bioactive secondary metabolites can potentially be found.

Many works summarize the specific beneficial effects of various *Chaetomium* species. Moya et al. (2020) highlighted the role of *Chaetomium globosum* in the agricultural industry as a plant growth promoter and a biocontrol agent, specifically in Argentina (Moya et al. 2020). A recent comprehensive study conducted in Saudi Arabia and Egypt focused on enlisting the *Chaetomium*-derived enzymes, such as L-methioninase, β-1,3-glucanase, laccase, dextranase, amylolytic, chitinolytic, and proteolytic enzymes, and their applications (Ibrahim et al. 2021). This study focused on the studies reported between 2016 and 2021 (Ibrahim et al. 2021). In another study, Tian et al. focused on bioactive compounds derived from marine *Chaetomium* species (Tian and Li 2022). Interestingly, they related the structure of the metabolites to their bioactivities, thus providing an unique insight into their biological functioning (Tian and Li 2022). Further, in mid-2022, a study on soil-derived *Chaetomium madrasense* 375 discussed various secondary metabolites, including chaetoviridins, chaetomugilins, and chaetoglobosin, isolated from the species (Guo et al. 2022).

This has encouraged us to prepare a comprehensive review on the bioactive compounds derived from various *Chaetomium* species. Various studies have tried to provide details on the *Chaetomium*-derived secondary metabolites and their multifarious application. However, this is perhaps one of the first reviews wherein an exhaustive compilation of data on the secondary metabolites from various *Chaetomium* strains, such as *C. globosum*, *C. cupreum, C. elatum*, *C. subspirale*, *C. olivaceum*, *C. indicum*, and *C. nigricolor*, with an insight into their origin and function, has been provided. A thorough literature survey (2000–2022) was conducted for obtaining *Chaetomium*-derived secondary metabolites, resulting in identification of more than 100 secondary

Table 1 A list of *Chaetomium*-derived bioactive compounds, along with their known bioactivity against various diseases/pathogens

Species	Metabolite	Metabolite class	Target	Tested system	Biological activity	Reference
Chaetomium globosum	Chaetone C	Dibenzoxepine	Various cancer	A549, Raji, HepG2, MCF-7, and HL-60 cell lines	IC_{50} values of 1.2, 1.8, 1.9, 2.3, and 1.6 µg/mL, respectively	(Shen et al. 2012)
	Chrysophanol	Trihydroxyanthraquinone	Cerebral ischemia	CD1 mice	Suppressed activation of NALP3 inflammasome	(Zhang et al. 2014)
	Chaetoglobosin A	Cytochalasan alkaloid	Colon cancer	HCT116 cell line	IC_{50} value of 3.15 µM	(Li et al. 2014)
	Chaetoglobosin F_a	Cytochalasan alkaloid	Colon cancer	HCT116 cell line	IC_{50} value of 5.85 µM	(Li et al. 2014)
	Chaetoglobosin A	Cytochalasan alkaloid	Myelogenous leukemia	K562 cells	IC_{50} value of 60 pM	(Ko et al. 1998)
	Armochaetoglosin C	Cytochalasan alkaloid	Bacterial activity	*Klebsiella pneumonia* and *Escherichia coli* ATCC 35,218	MIC = 4.0 µg/mL and 16.0 µg/mL, respectively	(Gao et al. 2019)
	Chaetomugilide A	Azaphilone alkaloid	Hepatocellular carcinoma	HePG2 cell line	IC_{50} value of 1.7 Mm	(Li et al. 2013)
	Chaetomugilide B	Azaphilone alkaloid	Hepatocellular carcinoma	HePG2 cell line	IC_{50} value of 19.8 µM	(Li et al. 2013)
	Chaetomugilide C	Azaphilone alkaloid	Hepatocellular carcinoma	HePG2 cell line	IC_{50} value of 53.4 µM	(Li et al. 2013)
	Chaetoviridin E	Azaphilone	Bacterial activity	*Staphylococcus aureus* and *Enterococcus faecalis*	MIC > 100 µg/mL	(Kingsland and Barrow 2009)
	Chaetoviridin B	Azaphilone	Bacterial activity	*Staphylococcus aureus* and *Enterococcus faecalis*	MIC > 100 µg/mL	(Kingsland and Barrow 2009)
	Chaetomugilin I	Azaphilone	Cancer	RAW 264.7 cells	IC_{50} value of 0.9 µM	(Youn et al. 2015)
	Chaetomugilin N	Azaphilone	Cancer	RAW 264.7 cells	IC_{50} value of 0.9 µM	(Youn et al. 2015)
	Chaetomugilin J	Azaphilone	Cancer	RAW 264.7 cells	IC_{50} value of 7.6 µM	(Youn et al. 2015)
	Chaetomugilin E	Azaphilone	Cancer	RAW 264.7 cells	IC_{50} value of 11.6 µM	(Youn et al. 2015)
	Chaetomugilin F	Azaphilone	Cancer	RAW 264.7 cells	IC_{50} value of 5.1 µM	(Youn et al. 2015)
	Chaetomugilin G	Azaphilone	Leukemia	P388 and HL-60 cell lines	IC_{50} value of 24.1 and 19.8 µM, respectively	(Yamada et al. 2009)
	Chaetomugilin H	Azaphilone	Leukemia and epithelial carcinoma	P388, HL-60 and KB cell lines	IC_{50} value of 4.1 and 19.8 µM, respectively	(Yamada et al. 2009)
	Chaetomugilin D	Azaphilone	Phytotoxic activity	*Lactuca sativa*	IC_{50} value of 24.2 ppm	(Piyasena et al. 2015)
	Chaetomugilin J	Azaphilone	Phytotoxic activity	*Lactuca sativa*	IC_{50} value of 22.6 ppm	(Piyasena et al. 2015)
	Chaetomugilin I	Azaphilone	Various cancer	39 human cancer cell lines	Potent selective cytotoxic activity	(Muroga et al. 2009)
	Chaetomugilin J	Azaphilone	Leukemia and epithelial carcinoma	P388, HL-60, L1210 and KB cell lines	IC_{50} value of 12.6, 12.6, 2.8, and 8.5 µM, respectively	(Muroga et al. 2009)
	Chaetomugilin K	Azaphilone	Leukemia and epithelial carcinoma	P388, HL-60, L1210 and KB cell lines	IC_{50} value of 8.2, 14.1, 11.2, and 18.7 µM, respectively	(Muroga et al. 2009)
	Chaetomugilin L	Azaphilone	Leukemia and epithelial carcinoma	P388, HL-60, L1210 and KB cell lines	IC_{50} value of 10.9, 13.1, 15.6, and 20.1 µM, respectively	(Muroga et al. 2009)
	Chaetomugilin N	Azaphilone	Leukemia and epithelial carcinoma	P388, HL-60, L1210 and KB cell lines	IC_{50} value of 2.3, 2.3, 10.6, and 10.6 µM, respectively	(Muroga et al. 2009)
	Chaetomugilin O	Azaphilone	Leukemia and epithelial carcinoma	P388, HL-60, L1210 and KB cell lines	IC_{50} value of 11.1, 11.1, 10.1, and 7.2 µM, respectively	(Muroga et al. 2009)

Table 1 (continued)

Species	Metabolite	Metabolite class	Target	Tested system	Biological activity	Reference
Chaetomium cupreum	Rotiorinol	Azaphilone	White root disease	*Rigidoporus microporus*	ED_{50} value of 26 µg/l	(Kaewchai and Soytong 2010)
	Rotiorinol A	Azaphilone	Fungal activity	*Candida albicans*	IC_{50} value of 10.5 µg/mL	(Kanokmedhakul et al. 2006)
	Rotiorinol C	Azaphilone	Fungal activity	*Candida albicans*	IC_{50} value of 16.7 µg/mL	(Kanokmedhakul et al. 2006)
	(-)-Rotiorin	Azaphilone	Fungal activity	*Candida albicans*	IC_{50} value of 24.3 µg/mL	(Kanokmedhakul et al. 2006)
	Rubrorotiorin	Azaphilone	Fungal activity	*Candida albicans*	IC_{50} value of 0.6 µg/mL	(Kanokmedhakul et al. 2006)
	Isochromophilonol	Azaphilone	Epithelial carcinoma	KB cell line	IC_{50} value of 9.63 µg/mL	(Panthama et al. 2015)
	Isochromophilonol	Azaphilone	Epithelial carcinoma	NCI-H187 cell line	IC_{50} value of 27.18 µg/mL	(Panthama et al. 2015)
	Ochrephilonol	Azaphilone	Epithelial carcinoma	KB cell line	IC_{50} value of 30.2 µg/mL	(Panthama et al. 2015)
	Clearanol B	α-Pyrone derivative	Epithelial carcinoma	KB cell line	IC_{50} value of 32.42 µg/mL	(Panthama et al. 2015)
	Clearanol B	α-Pyrone derivative	Breast cancer	MCF-7 cell line	IC_{50} value of 13.01 µg/mL	(Panthama et al. 2015)
Chaetomium elatum	Xanthoquinodin A4	Xanthoquinodin	Various cancer	SMMC-7721, A-549 and SW480 cell lines	IC_{50} value of 19.18, 25.47, and 18.85 µM, respectively	(Chen et al. 2013)
	Xanthoquinodin A5	Xanthoquinodin	Various cancer	HL-60, SMMC-7721, A-549, MCF-7, and SW480 cell lines	IC_{50} value of 26.62, 16.81, 18.60, 23.96, and 16.19 µM, respectively	(Chen et al. 2013)
	Xanthoquinodin A6	Xanthoquinodin	Various cancer	HL-60, SMMC-7721, A-549, MCF-7, and SW480 cell lines	IC_{50} value of 3.75, 2.87, 2.04, 5.64, and 6.44 µM, respectively	(Chen et al. 2013)
	Chaetomugilin S	Azaphilone	Apoptosis	Caspase-3	IC_{50} value of 20.6 µM	(Chen et al. 2012)
	7,5′-Bis-epi-chaetoviridin A	Azaphilone	Apoptosis	Caspase-3	IC_{50} value of 10.9 µM	(Chen et al. 2012)
	7-Epi-chaetoviridin E	Azaphilone	Apoptosis	Caspase-3	IC_{50} value of 7.9 µM	(Chen et al. 2012)
	Xanthoquinodin B4	Xanthoquinodin	Various cancer	HL-60, SMMC-7721, and A-549 cell lines	IC_{50} value of 3.01, 27.70, and 25.13 µM, respectively	(Chen et al. 2013)
	Xanthoquinodin B5	Xanthoquinodin	Various cancer	HL-60, SMMC-7721, and A-549 cell lines	IC_{50} value of 4.74, 14.99, and 11.38 µM, respectively	(Chen et al. 2013)
Chaetomium subspirale	Oxaspirodion	Spiro compound	Inflammatory activity	Jurkat T cells	IC_{50} value of 2.5 µg/ml	(Rether et al. 2004)
Chaetomium olivaceum	Myceliothermophin E	Polyketide	Microbial activity	Methicillin-resistant *Staphylococcus aureus* (MRSA)	MIC value of 15.8 µM	(Wang et al. 2020b)
	Chaetolivacine B	Polyketide	Microbial activity	Methicillin-resistant *Staphylococcus aureus* (MRSA)	MIC value of 27.1 µM	(Wang et al. 2020b)
	Chaetolivacine B	Polyketide	Microbial activity	*Staphylococcus aureus*	MIC value of 10.8 µM	(Wang et al. 2020b)
	Miliacin	Tritepenoid	Cytotoxic activity	Mouse erythrocytes	HC_{50} value of 2×10^{-4} mol/l	(Smetanina et al. 2001)
	Pseudoprotodioscin	Steroidal saponin	Cardiac disease	H9c2 cells	Increased the viability of H9c2, induced by H_2O_2, in a dose-dependent manner	(Dong et al. 2016)
	5-ene-3β, 20β-diol-22, 16-lactone-3-O-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside	Steroidal saponin	Cardiac disease	H9c2 cells	Increased the viability of H9c2, induced by H_2O_2, in a dose-dependent manner	(Dong et al. 2016)

Table 1 (continued)

Species	Metabolite	Metabolite class	Target	Tested system	Biological activity	Reference
	26-O-β-D-glucopyranosyl-23(S)-methoxyl-(25R)-furosta-5,20(22)-diene-3β,26-diol − 3-O-α-L-rhamnopyrano-syl-(1 → 4)-β-D-glucopyranoside	Steroidal saponin	Cardiac disease	H9c2 cells	Increased the viability of H9c2, induced by H_2O_2, in a dose-dependent manner	(Dong et al. 2016)
Chaetomium indicum	Chaetochromone A	Polyketide	Fungal activity	*Poria placenta* (Fr.) Cooke	> 60% inhibitory activity	(Lu et al. 2013)
Chaetomium nigricolor	(aS)-asperpyrone A	bis-naphtho-γ-pyrone	Inflammation	RAW 264.7 cells	Inhibited NO production	(Kim et al. 2020)
	(aS)-fonsecinone A	bis-naphtho-γ-pyrone	Inflammation	RAW 264.7 cells	Inhibited NO production	(Kim et al. 2020)
	Chamiside A	Cytochalasan	Bacterial activity	*Staphylococcus aureus*	MIC value of 25 μg/ml	(Wang et al. 2019)
Other Chaetomium sp.	Gliocladinin C	p-terphenyl glycoside	Larynx and hepatocellular carcinoma	Hep-2 and HepG-2 cell lines	IC_{50} value of 0.18 mM and 0.12 μM, respectively	(Han et al. 2019)
	Chaetominin A	Furano-polyene derivative	Larynx and hepatocellular carcinoma	Hep-2 and HepG-2 cell lines	IC_{50} value of 0.32 mM and 0.38 μM, respectively	(Han et al. 2019)
	Chaetocochin A	Epipolythiodioxopiperazine	Various cancer	Bre-04, Lu-04, and N-04 cell lines	GI_{50} value of 4.1, 3.4, and 7.0 μg/ml, respectively	(Li et al. 2006b)
	Chaetocochin C	Epipolythiodioxopiperazine	Various cancer	Bre-04, Lu-04, and N-04 cell lines	GI_{50} value of 0.4, 1.9, and 0.4 μg/ml, respectively	(Li et al. 2006b)
	Dethio-tetra (methylthio) chetomin	Thiodiketopiperazine alkaloid	Various cancer	Bre-04, Lu-04, and N-04 cell lines	GI_{50} value of 0.06, 0.05, and 0.2 μg/ml, respectively	(Li et al. 2006b)
	Mollicellin J	Depsidone	Various cancer	Bre-04, Lu-04, and N-04 cell lines	GI_{50} value of 5.9, 8.6, and 3.8 μg/ml, respectively	(Li et al. 2008)
	Mollicellin H	Depsidone	Various cancer	Bre-04, Lu-04, and N-04 cell lines	GI_{50} value of 5.1, 6.5, and 2.5 μg/ml, respectively	(Li et al. 2008)
	Mollicellin K	Depsidone	Malaria	*Plasmodium falciparum*	IC_{50} value of 1.2 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin L	Depsidone	Malaria	*Plasmodium falciparum*	IC_{50} value of 3.4 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin M	Depsidone	Malaria	*Plasmodium falciparum*	IC_{50} value of 2.9 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin B	Depsidone	Malaria	*Plasmodium falciparum*	IC_{50} value of 4.7 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin C	Depsidone	Malaria	*Plasmodium falciparum*	IC_{50} value of 9.1 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin E	Depsidone	Malaria	*Plasmodium falciparum*	IC_{50} value of 3.2 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin J	Depsidone	Malaria	*Plasmodium falciparum*	IC_{50} value of 4.9 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin K	Depsidone	Tuberculosis	*Mycobacterium tuberculosis*	MIC value of 12.5 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin K	Depsidone	Fungal activity	*Candida albicans*	IC_{50} value of 1.2 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin K	Depsidone	Epithelial carcinoma, breast cancer and small cell lung cancer	KB, BCI and NCI-H187 cell lines	IC_{50} value of 1.9, 6.8, and 0.35 μg/ml, respectively	(Khumkomkhet et al. 2009)
	Mollicellin L	Depsidone	Small cell lung cancer	NCI-H187 cell line	IC_{50} value of 9.5 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin M	Depsidone	Small cell lung cancer	NCI-H187 cell line	IC_{50} value of 0.68 μg/ml	(Khumkomkhet et al. 2009)
	Mollicellin N	Depsidone	Epithelial carcinoma and small cell lung cancer	KB and NCI-H187 cell lines	IC_{50} value of 25.9 and 13.5 μg/ml, respectively	(Khumkomkhet et al. 2009)
	Mollicellin B	Depsidone	Small cell lung cancer	NCI-H187 cell line	IC_{50} value of 14.7 μg/ml	(Khumkomkhet et al. 2009)

Table 1 (continued)

Species	Metabolite	Metabolite class	Target	Tested system	Biological activity	Reference
	Mollicellin C	Depsidone	Small cell lung cancer	NCI-H187 cell line	IC_{50} value of 3.1 µg/ml	(Khumkomkhet et al. 2009)
	Mollicellin E	Depsidone	Small cell lung cancer	NCI-H187 cell line	IC_{50} value of 1.0 µg/ml	(Khumkomkhet et al. 2009)
	Mollicellin F	Depsidone	Small cell lung cancer	NCI-H187 cell line	IC_{50} value of 13.1 µg/ml	(Khumkomkhet et al. 2009)
	Mollicellin H	Depsidone	Epithelial carcinoma and small cell lung cancer	KB and NCI-H187 cell lines	IC_{50} value of 16.6 and 3.9 µg/ml, respectively	(Khumkomkhet et al. 2009)
	Mollicellin J	Depsidone	Epithelial carcinoma and small cell lung cancer	KB and NCI-H187 cell lines	IC_{50} value of 29.1 and 23.3 µg/ml, respectively	(Khumkomkhet et al. 2009)
	Chaetosemin B	Chromone	Fungal activity	*Magnaporthe oryzae* and *Gibberella saubinettii*	MIC value of 6.25 and 12.5 µM, respectively	(Li et al. 2015)
	Chaetosemin C	Chromone	Oxidants	DPPH free radical scavenging activity	50.7% activity at 50 µM	(Li et al. 2015)
	Chaetoquadrin J	Chromone	Hypertension and Inflammation	Soluble epoxide hydrolase	IC_{50} value of 63.0 µM	(Li et al. 2015)
	Chaetocin	Piperazine	Bacterial activity	*Staphylococcus aureus*	MIC value of 0.1 µg/ml	(SAITO et al. 1988)
	Chaetocin B	Piperazine	Bacterial activity	*Staphylococcus aureus*	MIC value of 0.05 µg/ml	(SAITO et al. 1988)
	Chaetocin C	Piperazine	Bacterial activity	*Staphylococcus aureus*	MIC value of 0.025 µg/ml	(SAITO et al. 1988)
	Chetracin A	Epipolythiodioxopiperazine	Bacterial activity	*Staphylococcus aureus*	MIC value of 0.39 µg/ml	(SAITO et al. 1988)
	11α,11′α-Dihydroxychaetocin	Epipolythiodioxopiperazine	Bacterial activity	*Staphylococcus aureus*	MIC value of 0.2 µg/ml	(SAITO et al. 1988)
	Chaetocin	Piperazine	Cervical cancer	HeLa cells	IC_{50} value of 0.04 µg/ml	(SAITO et al. 1988)
	Chaetocin B	Piperazine	Cervical cancer	HeLa cells	IC_{50} value of 0.03 µg/ml	(SAITO et al. 1988)
	Chaetocin C	Piperazine	Cervical cancer	HeLa cells	IC_{50} value of 0.02 µg/ml	(SAITO et al. 1988)
	Chetracin A	Epipolythiodioxopiperazine	Cervical cancer	HeLa cells	IC_{50} value of 0.02 µg/ml	(SAITO et al. 1988)
	11α,11′α-Dihydroxychaetocin	Epipolythiodioxopiperazine	Cervical cancer	HeLa cells	IC_{50} value of 0.04 µg/ml	(SAITO et al. 1988)
	Radicicol	Macrolide	Breast cancer	MCF-7 cell line	IC_{50} value of 0.03 µM	(Turbyville et al. 2006)
	Chaetoquadrin G	Spiro compound	Depression	Monoamine oxidase inhibition in mouse liver	IC_{50} value of 0.045 µM	(Fujimoto et al. 2003)
	Chaetoquadrin H	Spiro compound	Depression	Monoamine oxidase inhibition in mouse liver	IC_{50} value of 0.023 µM	(Fujimoto et al. 2003)
	Mollipilin A	Polyketide	Colon cancer	HCT-116 cells	GI_{50} value of 1.8 µM	(Asai et al. 2012)
	Mollipilin B	Polyketide	Colon cancer	HCT-116 cells	GI_{50} value of 3.7 µM	(Asai et al. 2012)
	Sclerotiorin	Azaphilone	Hsp90 chaperoning activity	PR reconstitution assay	Inhibitory activity at par with known compounds	(Kabbaj et al. 2015)
	Chaetoatrosin A	*Naphthalene skeleton*	Fungal activity	*Rhizoctonia solani*	MIC value of 50 µg/ml	(Hwang et al. 2000)

metabolites with various beneficial properties, such as antitumor, cytotoxic, antimalarial, and enzyme inhibitory activities. The review spotlights the benefits of natural compounds and should supplement various drug development efforts.

Chaetomium-derived secondary metabolites

Secondary metabolites from Chaetomium globosum

Chaetomium globosum is a common mesophilic member of the *Chaetomiaceae* family of molds. It is a saprophytic fungus, which lives primarily on seeds, dirt, grass, and dung, and is also reported to live inside the plant tissue as an endophyte (Vivi et al. 2019). Their asymptomatic colonization confers tolerance to plants against toxicity from copper-like heavy metals, which inhibit plant production and disrupt metabolic processes such as photosynthesis. Abou Alhamed et al. 2012 reported that maize crop, upon administration with *Chaetomium globosum*, demonstrated increased biomass and lesser growth inhibition against metal toxicity (Abou Alhamed and Shebany 2012). *Chaetomium globosum* produces an array of biologically active compounds (Fig. 1) such as emodins (**1**), chrysophanols (**2**), chaetoglobosins A-G (**3–9**), isochaetoglobosin, chetomin (**11**), azaphilones (**12**), and chaetoviridins (**13–17**) (Madbouly and Abdel-Wareth 2020). Emodin (**1**) is an active component of many plants such as *Rheum palmatum*, *Polygonum cuspidatum*, and *Polygonum multiflorum*, which are used in traditional Chinese medicine. Emodin (**1**) reportedly exhibits laxative, antibacterial and anti-inflammatory effects (Akkol et al. 2021). Additionally, it might exhibit potential antiviral activity against SARS-CoV-2 (Horvat et al. 2021), being one of the most active components of Lianhua Qingwen, a traditional antiviral Chinese medicine formulation (Runfeng et al. 2020).

Chrysophanol (**2**) is an environmentally significant anthraquinone with wide-spectrum medicinal properties. Traditional Chinese and Korean medicinal systems provide evidence that chrysophanol (**2**) has important health benefits (Kikiowo et al. 2020). It is the first polyketide reported to be biosynthesized in an organism-specific way. Chrysophanol (**2**) exerts a therapeutic effect on cerebral ischemia – reperfusion (I / R) via its anti-inflammatory action. Zhang et al. (2014) reported that chrysophanol suppressed NALP3 inflammasome activation (which consists of NALP3, ASC, and caspase-1) for occlusion of the median cerebral artery (MCAO) and reperfusion (Zhang et al. 2014). Analysis of proteomic iTRAQ highlighted decorin (DCN) as another target of chrysophanol, while DCN knockdown considerably flouted chrysophanol-induced apoptosis in colorectal cancer (CRC) cells (Zhang et al. 2014). Taken together, chrysophanol exerts an anti-neoplastic effect under in vitro and in vivo conditions in CRC cells by modulating DCN, indicating its therapeutic potential in CRC cells (Zhang et al. 2014).

Chaetoglobosins (**3–9**) belong to cytochalasan alkaloids and constitute a large range of secondary fungal metabolites (Perlatti et al. 2020). Till date, more than 100 types of chaetoglobosins and their analogs have been isolated and characterized from a wide range of fungi, including *Chaetomium elatum* (Soytong et al. 2021), *Chaetomium globosum* (Darwish et al. 2020), *Phomopsis* sp. (Zhu et al. 2021), *Botryosphaeria dothidea* (Carvalho et al. 2019), and *Chaetomium subaffine* (Liu et al. 2021). Chaetoglobosins reportedly exhibit wide spectrum antitumor activity. They reportedly inhibited cell lines L929 (murine fibroblast cell line), KB3.1 (human epidermoid carcinoma cell line), PC-3 (human prostatic carcinoma cell line), and HUVEC (human umbilical vein endothelial cell line) with IC_{50} values of 1.6, 0.15, 0.42, and 0.78 µg/mL, respectively (Flewelling et al. 2015). Li et al. (2014) reported cytotoxic effect of chaetoglobosins towards HL60 (human promyelocytic cell line), A549 (hypotriploid human cell line), SMMC7721 (human hepatocarcinoma cell line), MCF-7 (human breast cancer cell line), and SW480 (human colon cancer cell line) cell lines with an inhibitory activity ratio range of 51–96% at 40 µmol/L (Li et al. 2014). In addition, MDA-MB-435 (human breast cancer cell line), SGC-7901 (human gastric cancer cell line), and A549 cell lines were found to be inhibited with IC_{50} values of 4.65, 5.32, and 8.73 µmol/L, respectively (Tikoo et al. 1999).

In 2013, Zhang et al. reported that chaetoglobosin A (**3**), C (**5**), D (**6**), E (**7**), G (**9**) and R (**10**) can inhibit the growth of two phytopathogenic fungi, *Rhizopus stolonifer* and *Coniella diplodiella* (Zhang et al. 2013). Multiple studies have shown that there is significant antibacterial potential of chaetoglobosins towards agricultural pathogens. Zhu et al. (2017) displayed that penochalasin K, a novel chaetoglobosin isolated from *Penicillium chrysogenum* V11, had an effective antimicrobial activity towards *Colletotrichum gloeosporioides*, with an IC_{50} value of 6.13 µmol/L (Zhu et al. 2017). Gao et al. (2019) reported a stronger antimicrobial activity of armochaetoglobosin C, a 1′-N-methyl-chaetoglobosin, towards *Klebsiella pneumoniae* (MIC = 4.0 µg/mL) as compared to commonly used antibiotic meropenem (MIC = 8 µg/mL) (Gao et al. 2019). All these reports point at potential application of these compounds in agricultural and clinical aspects.

Chetomin (**11**), a metabolite compound produced by genus *Chaetomium*, was reported to inhibit tumor growth via blockade of hypoxia-inducible transcription (Telarovic et al. 2021). Chetomin (**11**) changes the confirmation of CH1 domain of p300, a transcriptional coactivator, thereby reducing the communication between p300 and HIF-1α (Telarovic et al. 2021). Li et al. (2013) isolated three novel endophytic *Chaetomium globosum* TY1 azaphilone alkaloids, namely chaetomugilides A–C (**18–20**), that reported high cytotoxic

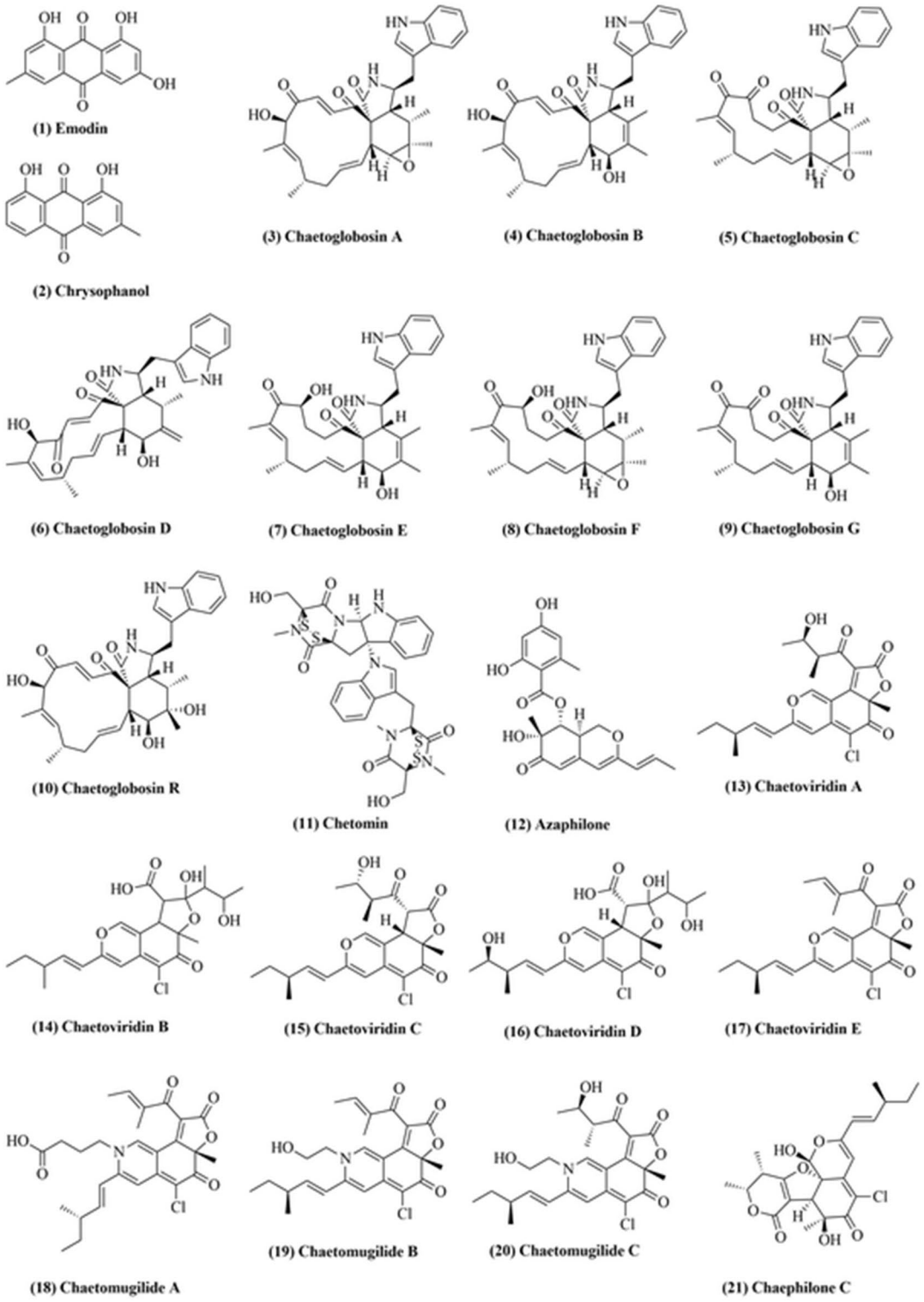

Fig. 1 Some of the compounds isolated from *Chaetomium globosum*

activity towards HePG2 (human cancer cell line) with IC_{50} values ranging from 1.7 to 53.4 μM (Li et al. 2013). Two phytotoxic azaphilone derivatives, chaetomugiline D and chaetomugiline J, isolated from *Amaranthus viridis* derived *C. globosum* exhibited phytotoxic activity in seed germination bioassay of *Lactuca sativa* (Piyasena et al. 2015). The root growth inhibition IC_{50} values of chaetomugiline D and chaetomugiline J were 24.2 and 22.6 ppm, respectively,

whereas the shoot growth inhibition IC_{50} values were 27.8 and 21.9 ppm, respectively (Piyasena et al. 2015). Recently, a novel azaphilone, chaephilone C (**21**), isolated from *Polygonatum sibiricum* derived *C. globosum* displayed cytotoxicity against HepG-2 cells with IC_{50} values of 38.6 µM (Song et al. 2020).

In 1990, Takahashi et al. extracted four novel azaphilones, namely chaetoviridins A–D (**13–16**), from *C. globosum* culture and reported their structure (TAKAHASHI et al. 1990). In 2009, a revised structure of chaetoviridin B and D was proposed, along with the structure of chaetoviridin E (**17**) (Kingsland and Barrow 2009). Youn et al. (2015) isolated two novel azaphilones, chaetoviridins J and K, from *Wikstroemia uva-ursi* derived *C. globosum* (Youn et al. 2015). Chetoviridin J presented encouraging results when assessed for cancer chemo-preventive-potential based on the capacity to prevent TNF-α-induced nuclear factor-kappa B (NF-κB) (Youn et al. 2015).

Secondary metabolites from Chaetomium cupreum

Chaetomium cupreum, a member the family, *Chaetomiaceae*, can grow on synthetic cellulosic materials and is known to infect a broad variety of soil microorganisms. *C. cupreum* is mesophilic and rapidly colonizes organic substances in soil (Dionizio et al. 2022). Broad spectrum fungicides obtained from several *C. cupreum and C. globosum* strains reportedly induce tolerance against *Phytophthora palmivora*, *Phytophthora parasitica*, *Fusarium oxysporum*, and *Sclerotium rolfsii* (Soytong et al. 2021). Also, *C. cupreum* RY202 crude extracts in hexane, ethyl acetate, and methanol with ED_{50} values of 170, 402, and 1220 µg/L, respectively, prevent the growth of *Rigidoporus microporus*, the causative agent of white root disease in rubber trees (Kaewchai and Soytong 2010). Moreover, rotiorinol, a bioactive compound formed by *C. cupreum*, inhibits the growth of *R. microporus* with ED_{50} value of 26 µg/L (Kaewchai and Soytong 2010).

In 2006, three novel azaphilones, rotiorinols A-C (**22–24**; Fig. 2), and two additional stereoisomers, (-)-rotiorin (**25**) and epi-isochromophilone II (**26**), were isolated from *C. cupreum* (Kanokmedhakul et al. 2006). Rotiorinol A (**22**), C (**24**), and (-)-rotiorin (**25**) displayed strong antifungal activity against *Candida albicans* with IC_{50} values of 10.5, 16.7, and 24.3 µg/mL, respectively (Kanokmedhakul et al. 2006). In 2015, two novel angular azaphilone forms, isochromophilonol and ochrephilonol, were isolated from *C. cupreum* (Panthama et al. 2015). Both novel compounds displayed mild cytotoxicity against KB (epidermoid carcinoma) and NCI-H187 (lung cancer) cell lines, with IC_{50} value ranging between 9.63 and 32.42 µg/mL (Panthama et al. 2015).

In vitro analysis suggested that *C. cupreum*, *C. globosum* and *C. lucknowense* induce an inhibitory effect on growth parameters of *Phytophthora palmivora*, the causative organism of root rot in *Citrus maxima* (Hung et al. 2015). In another experiment, *C. cupreum* extracts in hexane, ethyl acetate and methanol demonstrated substantial inhibition of *Colletotrichum gloeosporioides* (an anthracnose pathogen), with ED_{50} values of 13, 11, and 28 ppm, respectively (Vilavong and Soytong 2017). In addition, use of powdered, nano-rotiorinol, nano-trichotoxin, and a spore suspension of *C. cupreum* reduced anthracnose by 54.77%, 46.23%, 42.71%, and 18.59%, respectively (Vilavong and Soytong 2017). An analysis of antioxidant properties of different organic solvent extracts of *C. cupreum* was conducted by Wani and Tirumale (2018) by employing multiple antioxidant assays (Wani and Tirumale 2018). The results indicated at significant antioxidant activity of *C. cupreum* and warranted further experimental evaluation (Wani and Tirumale 2018).

Secondary metabolites from Chaetomium elatum

Chaetomium elatum is a significant saprotrophic mold-fungus of the *Chaetomiaceae* family, believed to grow on many different substances worldwide (Moya et al. 2020). It was discovered by Gustav Kunze on dead leaves. The distinguishing characteristic of this fungus is its extremely coarse coating.

C. elatum has been isolated from various products, and many studies have investigated its biochemical properties for possible biotechnological applications. Thohinung et al. (2010) extracted anticancer fungal 10-(Indol-3-yl)-[13] cytochalasans from endophytic *C. elatum*, reporting possible cytotoxicity against human breast cancer (IC_{50} 2.54–21.29 µM) and cholangiocarcinoma (IC_{50} 3.41–86.95 µM) cell lines (Thohinung et al. 2010). In 2012, three new azaphilones, chaetomugilin S (**27**; Fig. 2), 7,5′-bis-epi-chaetoviridine A and 7-epi-chaetoviridine E were isolated from *C. elatum* raw extract (Chen et al. 2012). These three compounds were the first examples of 7R-configured azaphilones with a chlorinated isochromen, found in *Chaetomium* species. They displayed inhibitory activity in the caspase-3 enzymatic assay, with IC_{50} values of 20.6, 10.9, and 7.9 µM, respectively (Chen et al. 2012). Additionally, two new chlorinated phenolic glycosides, globosumoside A (**28**) and globosumoside B (**29**), were also isolated (Chen et al. 2012). In yet another study, five new xanthoquinodins, A4-A6 (**32, 33**), B4 (**34**), and B5 (**35**), along with three existing xanthoquinodins, A1-A3 (**30, 31**), were isolated from methanolic extracts of the endolichenic fungal strain *C. elatum* (Chen et al. 2013). The cytotoxic activity of all compounds was tested against various human cancer cell lines (HL-60, SMMC7721, A-549, MCF-7, and SW480), and xanthoquinodin A6 displayed significant activity with IC_{50} values of 3.75, 2.87, 2.04, 5.64, and 6.44 µM, respectively (Chen et al. 2013).

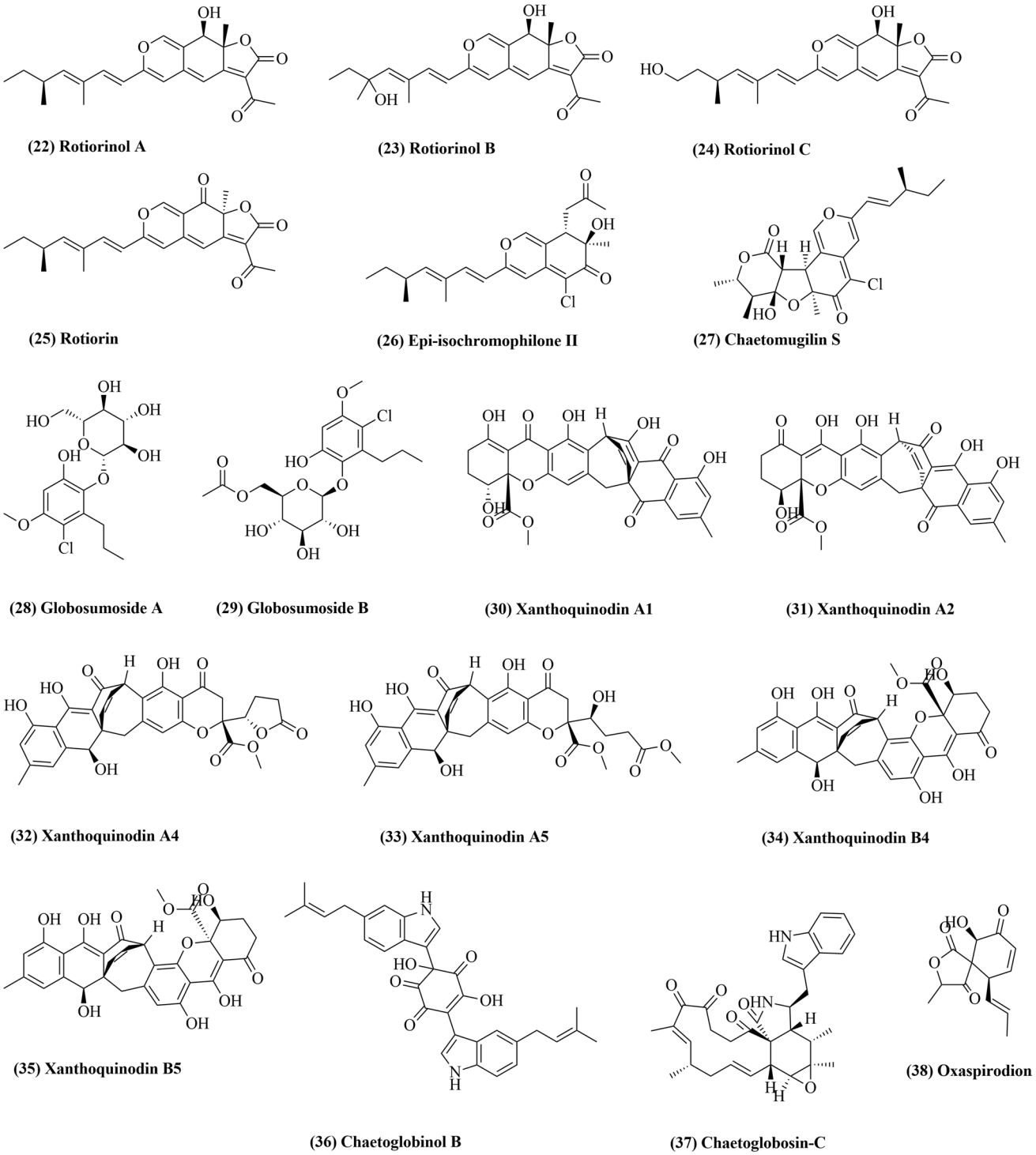

Fig. 2 Some of the compounds isolated from *Chaetomium cupreum* (22–26), *Chaetomium elatum* (27–37), and *Chaetomium subspirale* (38)

In 2019, Yao et al. isolated a new compound, chaetoglobinol B (**36**), from *C. elatum* solid-state fermented rice culture (Yao et al. 2019). It reportedly inhibited α-glycosidase at a 2.5 mg/mL concentration (Yao et al. 2019). A highly virulent isolate from *Fusarium oxysporum* f. sp. Lycopersici, responsible for causing wilt of tomato, was reported to be effectively inhibited by *C. elatum*, *C. lucknowense*, and *Emericella rugulosa* strains (Sibounnavong et al. 2011). Chaetoglobosin-C (**37**) was identified as the compound responsible for antifungal activity, with

ED_{50} of 5.98 µg/ml (Sibounnavong et al. 2011). The study further indicated that antibiosis was involved in the process of disease prevention by these antagonistic fungi.

Secondary metabolites from Chaetomium subspirale

Chaetomium subspirale fungi belongs to phylum *Ascomycota* (Netz 2019). It was discovered by A.H. Chivers in 1912, America. The organism has sexual fruiting bodies decorated with signature, coiled hairs, which give it a puffy look. *C. subspirale* has brown colored colonies and is usually found in various types of soil and dung (Attia and Abdel-Azeem 2020).

C. subspirale generates mycotoxin oxaspirodion (**38**; Fig. 2) that inhibits TNF expression and stimulation of the NF-κB transcription factor (Abdel-Azeem et al. 2019). Oxaspirodion (**38**) inhibits the expression of the TNF-α-driven luciferase reporter gene with an IC_{50} value of 2.5 µg/ml in TPA-/ionomycin-stimulated Jurkat T-cells by intervening in phosphorylation of the ERK1/2 kinases (Abdel-Azeem et al. 2019). In addition, oxaspirodion (**38**) also inactivated the transcription factor NF-κB, which is implicated in inducible expression of several pro-inflammatory genes (Abdel-Azeem et al. 2019).

Secondary metabolites from Chaetomium olivaceum

In 1961, a report stated that after a week at 21 °C, a culture of *Chaetomium* fruited on Pablum-cereal-agar abundantly, and it was described as being nearest to *Chaetomium olivaceum* (Маслиенко 2019).

In 2003, El-Gindy and Saad purified enzyme exo-1,4-beta-glucanase from *C. olivaceum*, achieving 72.8% yield (El-Gindy et al. 2003). The enzyme's optimum pH was reported to be 5.2, while maximal activity was at 45 °C. Km value was 0.65 mg/mL against alpha-cellulose (El-Gindy et al. 2003). Recently, three new polyketides, Chaetolivacines A–C, and one known compound, myceliothermophin E (**39**; Fig. 3), were isolated from *C. olivaceum* (Wang et al. 2020b). Chaetolivacines B and myceliothermophin E (**39**) displayed moderate activity when tested against *Staphylococcus aureus* for their antibacterial properties (Wang et al. 2020b).

Five novel pseudoprotodioscin (**40**) derivatives were obtained via pseudoprotodioscin transformation by *C.* (Dong et al. 2016). Pseudoprotodioscin and its derivatives were examined for their beneficial role against H_2O_2-mediated myocardial cell injury. It was confirmed that a few derivatives improved the efficacy of H9c2 mediated by H_2O_2 in the concentration range from 3125 to 25 g/mL in a dose-dependent way (Dong et al. 2016).

Secondary metabolites from Chaetomium indicum

The *Chaetomium indicum* group has ascomata hair branched dichotomously (Kedves et al. 2021). The presence of multiple hair variant types has complicated the classification of *C. indicum* and related organisms. Skolko and Grover (1948) focused on the presence/absence of branched hair characters and unbranched terminal hairs (Wang et al. 2016). Burtseva et al. (2000) successfully isolated beta-1,3-glucanase from marine *C. indicum* (Burtseva et al. 2000).

Li et al. (2006a, b) isolated Chaetoindicins A – C (**41–43**; Fig. 3), three isoquinolines with novel skeletons, from a fermented solid-state culture of *C. indicum* (Li et al. 2006a). Two novel spironolactone polyketides, spiroindicumides A (**44**) and B (**45**), were isolated from *C. indicum* with the help of histone deacetylase inhibitor (Asai et al. 2013). In 2013, two novel polyketides, Chaetochromones A (**46**) and B (**47**), were discovered along with three known analogs, PI-3, PI-4, and SB236050, from the crude fungal extract of *C. indicum* (Lu et al. 2013). The biological activities of all the isolated bioactive compounds was tested against eight plant pathogens, namely *Alternaria alternata*, *Ilyonectria radicicola*, *Trichoderma viride pers*, *Aspergillus niger*, *Fusarium verticillioides*, *Irpex lacteus (Fr.)*, *Poria placenta (Fr.) Cooke*, and *Coriolus versicolor (L.) Quél* (Lu et al. 2013). Chaetochromone A (**46**) showed high inhibitory activity (> 60%) against *Poria placenta (Fr.) Cooke*, a brown rot fungus responsible for wood decay (Lu et al. 2013). However, the cytotoxic activities were also tested against A549, MDA-MB-231, and PANC-1 cancer cell lines, without finding any inhibitory activities (Lu et al. 2013).

Secondary metabolites from Chaetomium nigricolor

Chaetomium nigricolor is similar to *Ovatospora* members, with respect to ascospore morphology (Abdel-Azeem et al. 2021). *C. nigricolor* ascopore differs in being attenuated at one end and apiculate at the other end, while *Ovatospora* ascopores are attenuated at one and round at the other end (Abdel-Azeem et al. 2021).

Chamiside A, a novel cytochalasan with a new 6/6/5-fused tricyclic core skeleton, was isolated from *Mahonia fortunei* derived *C. nigricolor* (Wang et al. 2019). Chamiside A was found to display antibacterial activity against *Staphylococcus aureus* (Wang et al. 2019). In another study, *Catharanthus roseus* derived *C. nigricolor* was reported to exhibit potent cytotoxic, apoptotic, and antioxidant properties (Dhayanithy et al. 2019). Recently, twelve secondary metabolites from *C. nigricolor* were isolated, including a new furan derivative, methyl succinyl-sumiki's acid, and two novel atropisomers of bis-naphtho-γ-pyrones, (a*S*)-asperpyrone A (**48**; Fig. 3) and (a*S*)-fonsecinone A (**49**) (Kim et al. 2020). The two atropisomers inhibited nitric oxide

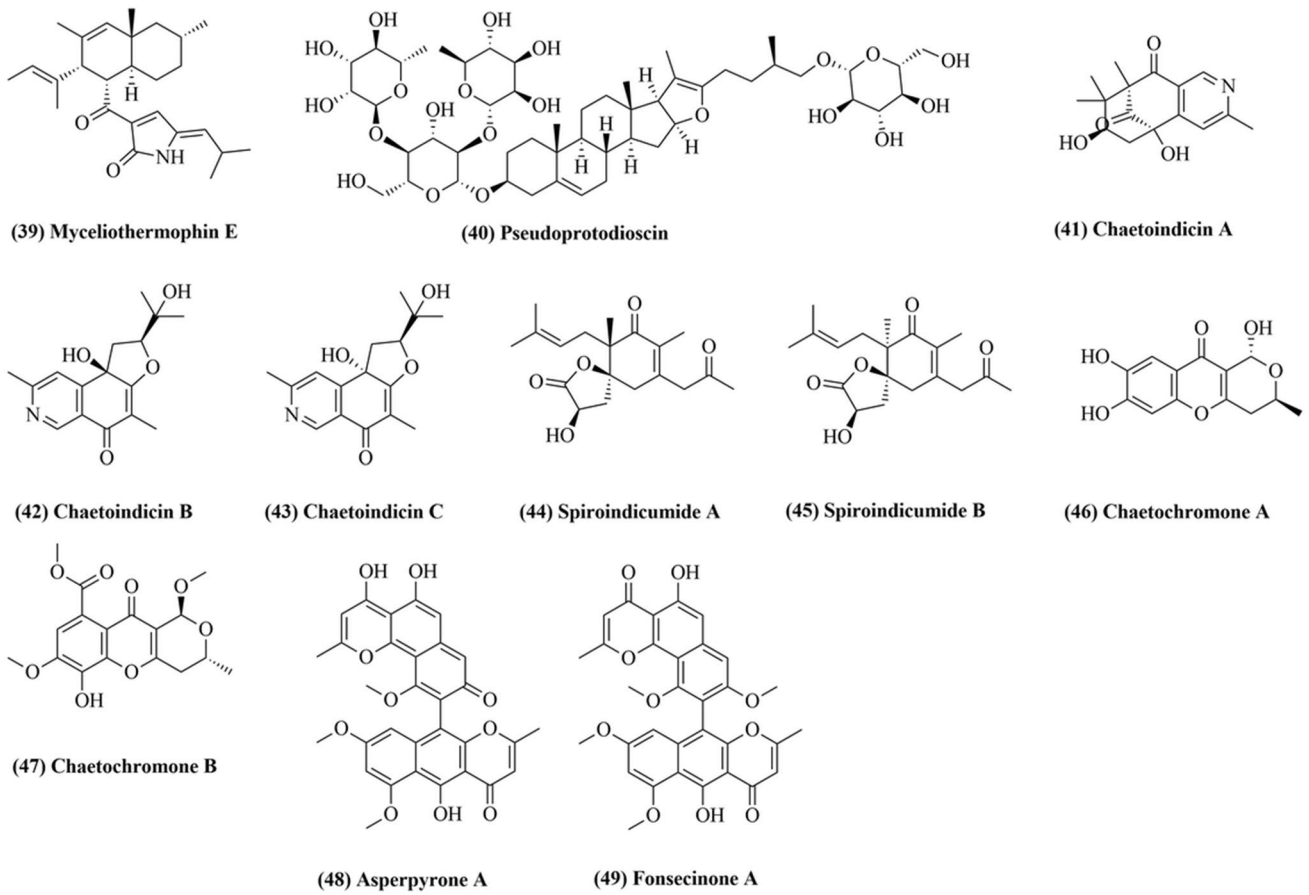

Fig. 3 Some of the compounds isolated from *Chaetomium olivaceum* (39, 40), *Chaetomium indicum* (41–47), and *Chaetomium nigricolor* (48, 49)

production in lipopolysaccharide-stimulated RAW 264.7 macrophages (Kim et al. 2020). Additionally, (aS)-asperpyrone A (**48**) reportedly inhibited NF-κB, consequently, suppressing pro-inflammatory mediators and cytokine release (Kim et al. 2020).

Secondary metabolites from other Chaetomium sp

In 1992, precursors of chaetoglobosin A, viz., prochaetoglobosins I, II, III, and IV, were isolated from *Chaetomium subaffin*, an endophytic potato fungus (Oikawa et al. 1992). In another study, *C. subaffin* was used to isolate gliocladinin C (a natural p-terphenyl glycoside) and two furano-polyene derivatives, chaetominins A (**50**; Fig. 4) and B. Gliocladinin C and chaetominin A (**50**) reportedly inhibited human tumor cell lines, Hep-2 and HepG-2 (Han et al. 2019).

Recently, Wang et al. (2020a, b) extracted nine novel epipolythiodioxopiperazine analogs, chetocochliodins A-I (**51–54**), along with two existing ones, chetoseminudins E and C, from *Chaetomium cochliodes* (Wang et al. 2020a). Chetocochliodin I was shown to inhibit cancerous cell lines (Wang et al. 2020a). In another study, the same group worked on *C. cochliodes* and reported cytotoxic activity of four novel chetomin analogues, chetomins A–D (**56, 57**), against HepG2, MCF-7, and HeLa cancer cell lines (Wang et al. 2018). In 2006, three new epipolythiodioxopiperazines, chaetocochins A–C (**58–60**), along with dethio-tetra (methylthio) chetomin (**61**) and chetomin, were obtained from *C. cochliodes* (Li et al. 2006b). Chaetocochin A (**58**), C (**60**) and chetomin demonstrated substantial inhibitory activity towards Bre-04 (breast cancer), Lu-04 (lung cancer), and N-04 (neuroma) cell lines (Li et al. 2006b).

An ethyl acetate extract of *Chaetomium brasiliense* was used to isolate three novel compounds, mollicellin I (**62**; Fig. 4), mollicellin J (**63**), and 2-(hydroxymethyl)-6-methylmethyleugenin, along with six known compounds, mollicellin D (**64**), mollicellin H (**65**), eugenetin (**66**), o-methylsterigmatocystin (**67**), sterigmatocystin (**68**), and chaetocin (**69**) (Li et al. 2008). Mollicellins I (**62**) and H (**65**) demonstrated inhibitory activity against three human cancer cell lines, Bre-04, Lu-04, and N-04, with GI_{50} in the range of 2.5–8.6 μg/mL (Li et al. 2008). In another report, four novel compounds, mollicellins K-N (**74–77**), and six known compounds, mollicellins B (**70**), C (**71**), E (**72**), F (**73**), H

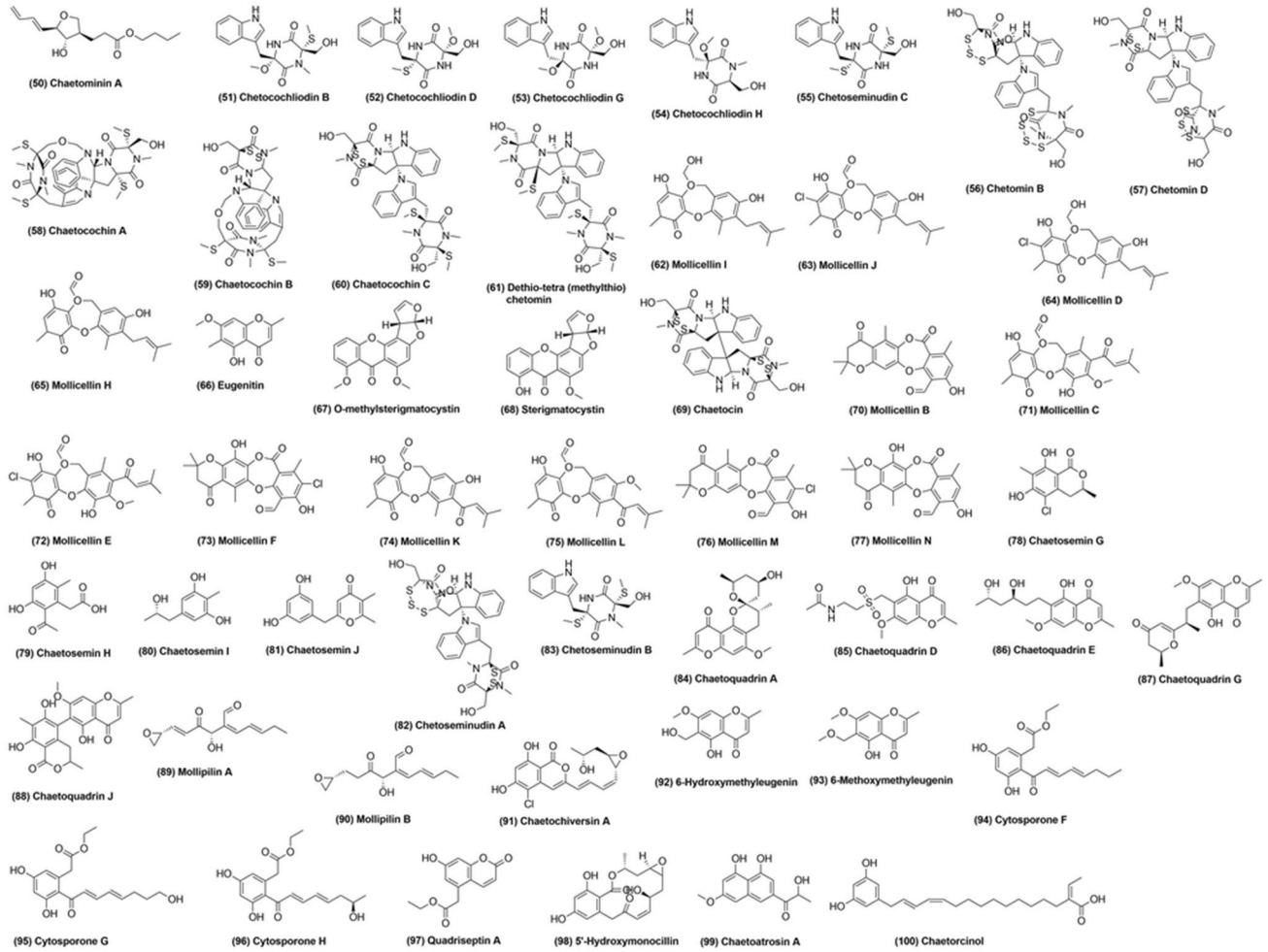

Fig. 4 Some of the compounds isolated from various *Chaetomium* species

(**65**), and J (**63**), were derived from *C. brasiliense* and exhibited cytotoxic activity against various cancerous cell lines (Khumkomkhet et al. 2009). In addition, mollicellin K (**74**) also displayed antimycobacterial and antifungal activities against *Mycobacterium tuberculosis* and *Candida albicans*, respectively (Khumkomkhet et al. 2009). Interestingly, mollicellins B (**70**), C (**71**), E (**72**), J (**63**), K (**74**), L (**75**), and M (7**6**) were reported to exhibit antimalarial activity against *Plasmodium falciparum* (Khumkomkhet et al. 2009).

Li et al. (2018) isolated numerous secondary metabolites from *Chaetomium seminudum* and suggested monaschromone as a potent pesticide based on in vitro analysis (Li et al. 2018). Also, they reported epicoccone B and falvipin as better α-glucosidase inhibitors as compared to the standard drug acarbose (Li et al. 2018). Four novel compounds, chaetosemins G-J (**78–81**), were also isolated during the same study and chaetosemin J (**81**) was found to inhibit various plant pathogenic fungi such as *Botrytis cinerea*, *Alternaria solani*, *Magnaporthe oryzae*, and *Gibberella saubinettii* (Li et al. 2018). In 2004, three novel metabolites, chetoseminudins A (**82**), B (**83**), and C (**55**), were isolated from *C. seminudum* along with the known epipolythiodioxopiperazine, chetomin (Fujimoto et al. 2004). Chetoseminudin A (**82**) and chetomin were found to be responsible for the characteristic immunosuppressive features of *C. seminudum* (Fujimoto et al. 2004).

Eleven chaetoquadrins were derived from an EtOAc extract of ascomycetes *Chaetomium quadrangulatum* by Fujimoto et al. (2003) (Fujimoto et al. 2003). Off them, five (chaetoquadrins A-E; **84–86**) were previously reported by the same group (Fujimoto et al. 2002), while six novel compounds (chaetoquadrins F-K; **87, 88**) were found in this study (Fujimoto et al. 2003). Chaetoquadrins A–E, G, and H were found to exhibit monoamine oxidase inhibitory activity (Fujimoto et al. 2002, 2003). In 2012, *Chaetomium mollipilium* culture, in the presence of nicotinamide, a HDAC inhibitor, led to isolation of five novel C_{13}-polyketides, mollipilin A–E (**89, 90**) (Asai et al. 2012). Mollipilins A (**89**) and B (**90**) were reported to mildly inhibit human colon cancer cell line, HCT-116 (Asai et al. 2012).

Two new isocoumarins, chaetochiversins A (**91**) and B, and four known compounds radicicol, 6-hydroxymethyleugenin (**92**), eugenetin (**66**), and 6-methoxymethyleugenin (**93**), were identified from the endophyte *Chaetomium chiversii* as Hsp90 inhibitors (Turbyville et al. 2006; Wang et al. 2008; Wijeratne et al. 2006). Chaetoatrosin A (**99**), a novel inhibitor of chitin synthase II (IC_{50} = 104 µg/ml), was isolated from *Chaetomium atrobrunneum* and reportedly displayed antifungal activity against *Rhizoctonia solani*, *Pyricularia oryzae*, *Botrytis cinerea*, *Cryptococcus neoformans*, and *Trichophyton mentagrophytes* (Hwang et al. 2000). In another interesting study, two novel, thermostable β-glucosidases of the GH3 family, were isolated from *C. atrobrunneum* and suggested as enzyme mixture components for better cellulose saccharification at high temperatures (Colabardini et al. 2016). Kabbaj et al. (2015) successfully isolated a novel compound, chaetorcinol (**100**), along with five known compounds, (+)-sclerotiorin, (+)-sclerotioramin, (+)-isochromophilone IV, (+)-isochromophilone VII, and SB 236,050 (Kabbaj et al. 2015). Sclerotiorin was reported to be an efficient Hsp90 inhibitor, while deacetylated sclerotiorin displayed inhibitory activity towards breast cancer (Hs578T, MDA-MB-231) and prostate cancer (LNCaP) cell lines (Kabbaj et al. 2015).

Conclusion and future perspectives

More than 200 bioactive compounds, belonging to various classes such as azaphilones, cytochalasan alkaloids, hydroxyanthraquinones, polyketides, xanthoquinodin, glycosides, spiro-compounds, terpenoids, steroid saponin, and chromones, have been discovered as secondary metabolites in various *Chaetomium* species. These compounds are known to exhibit anticancer, antiviral, antibacterial, and antifungal activities, making them potential candidates for therapeutic and drug development efforts. However, there are many challenges in studying *Chaetomium* species. Firstly, multiple species are known to dwell in different environments, leading to difficulties in procurement and fermentation. Also, large-scale extraction of bioactive compounds is required for validation of their activity in animal models. Moreover, determining and analyzing the stereochemistry of isolated bioactive compounds may prove to be tedious. Additionally, once the structure has been determined, it is a tough ask to extrapolate it to the various known activities of the compound. Also, new strategies need to be developed to analyze and optimally interpret the interaction between *Chaetomium* and other species.

Despite these hurdles, further research on *Chaetomium* species might elucidate yet unknown secondary metabolites. A deeper analysis of their biosynthetic pathways, pharmacokinetic properties, structure–activity relationships, mechanism of action, and ecological roles might highlight more candidates against multiple cancers and other disorders.

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Author contribution VD: Original draft preparation. SKR: Conceptualization; methodology; supervision. SJ: Review and editing; formal analysis and investigation. NMA: Formal analysis and investigation. RP: Review and editing. SS: Review and editing. LRS: Conceptualization; methodology; supervision.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

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